BACKGROUND/STATEMENT OF WORK

1. Background Information

The Chemopreventive Agent Development Research Group (CADRG) of the Division of Cancer Prevention directs an applied research & development program to qualify agents for and to conduct clinical trials to prevent, reverse, and delay carcinogenesis prior to invasive disease.

The research programs, aimed at chemopreventive agent development and evaluation, function in accord with Federal regulations enforcing adherence to current Good Laboratory Practices, current Good Manufacturing Practices, and Investigational New Drug studies.

A. The Preclinical Program of the DCP CADRG includes *in vitro, in vivo,* efficacy, intermediate endpoints and pharmacology and toxicology program components:

1. *In Vitro* Screening Program

This program evaluates potential chemopreventive activities of new agents in a number of biochemical, cell, and tissue models associated with carcinogenesis:

a. cell transformation bioassays
b. mechanistic biochemical assays
c. modulation of intermediate preneoplastic biological markers
d. hyperplastic nodule formation assays

2. *In Vivo* Screening Program

This program provides the initial evidence of positive chemopreventive activity for an agent in animal models of carcinogenesis:

a. establishes initial dose - response relationship
b. provides evidence of agent acceptability and tolerance in animals
c. provides initial evidence of agent toxicity

3. *In Vivo* Efficacy Program

This program establishes the chemopreventive efficacy of an agent in preparation for clinical evaluation:

a. confirmation of chemopreventive activity against tumor incidence and multiplicity
b. further refinement of dose - response relationship

c. chronic evaluation of systemic physiological reactions to agent
d. indication for further testing in combination with another agent to lower toxicity & improve efficacy

4. Intermediate Endpoint Evaluation

This program evaluates potential intermediate endpoints in carcinogenesis that might be used in clinical trials.

a. Biomarkers of risk and exposure dosimetry
b. Pharmacological markers of agent mechanisms
c. Causal and associative biomarkers of carcinogenesis

5. Preclinical Pharmacology, Toxicology and Safety Evaluation

This program focuses on tests required by the FDA to qualify an agent as safe for human trials:

a. mutagenicity tests
b. acute, subchronic, and chronic toxicity
c. carcinogenicity evaluation
d. reproductive performance & teratogenicity tests
e. absorption, distribution, metabolism, & elimination studies
f. specialized studies, such a neurological & immunological evaluations

B. The above five program areas support the qualification of agents for clinical development and evaluation. To this end, there are additional support programs operating in the CADRG of the Division of Cancer Prevention.

1. Phase 1 Clinical Trials Program

The goal of Phase 1 studies is to evaluate the pharmacokinetics, pharmacology, and toxicology of chemopreventive agents in humans. Various doses, well below that extrapolated from preclinical toxicity findings, are evaluated. Healthy human subjects, who are usually at increased risk for cancer, are eligible for Phase I studies.

2. Phase 2 Clinical Trials Program

The goal of Phase 2 studies is to evaluate further the pharmacology, efficacy, & safety of chemopreventive agents. Pharmaceutical dosages of agents are selected based on the safety profile developed in Phase 1 studies. The pharmacological endpoint is to modulate surrogate intermediate biochemical/biological markers hypothesized to be early indicators of the carcinogenic process or neoplastic state. Human subjects who have or have had cancer and are at high risk for recurrence and/or neoplastic lesions are evaluated in Phase 2 studies.

3. Phase 3 Clinical Trials Program

The goal of Phase 3 trials is to conduct large-scale human intervention studies in which chemopreventive agents are administered for long periods of time. The final assessment of chemopreventive agent efficacy is tumor multiplicity and latency, malignancy, morbidity, mortality, and demonstration of reduction of cancer risk. Human subjects at high risk for cancer are enrolled in Phase 3 trials.

C. Four critical research support activities sustain the planning, information management, regulatory, quality assurance, and drug supply components of chemopreventive studies at both the preclinical and clinical levels.

1. Scientific Information Gathering, Analysis, Review, and Planning Support

This program is a multidisciplinary activity to assist the CADRG with evaluation of the world literature for potential chemopreventive agents. Specific emphasis is placed on factors to prioritize agents for clinical drug development and on data management and assimilation needs. Activities in this program are essential for program planning, interfacing with consultants to the DCP, bridging the gaps in knowledge between preclinical and clinical studies, drug development, and interaction with other Federal agencies and the private sector.

2. Regulatory Support

This program provides support for the initial filing and maintenance of Investigational New Drug applications by the NCI DCP to the FDA. Activities include compilation of documentation for an IND filing - including preclinical efficacy & toxicity data; chemistry, manufacturing, & control information; clinical protocol(s), clinical investigator signatures, informed consent, IRB approval, etc.; and

supporting references - and submission of the IND. FDA correspondence, IND file maintenance, and annual report summaries are also supported.

3. Clinical Trial Monitoring Support

This program is conducted through a Clinical Research Organization. NCI-funded and IND-sponsored trials are audited for procedural compliance with FDA regulations for human clinical studies and for data completeness and accuracy. Documentation related to protocol amendments, adverse event reporting, and interaction with NCI medical monitors is supported.

4. Centralized Chemopreventive Agent Repository Support

A complete description of this activity is found in following statement of work and is the focus of this RFP.

Statement of Work

The contractor shall furnish services, qualified personnel, materials, supplies, equipment and facilities under the terms of this contract as needed to perform the work described.

I. General Requirements

The object of this project is to establish a centralized source of agents for use in preclinical and clinical studies by the Division of Cancer Prevention of the National Cancer Institute (NCI) and to perform certain agent-related pharmaceutical characterization, formulation, & documentation activities. For preclinical & clinical studies, the project would provide: identification of sources and procurement (purchase and/or synthesis) of bulk reagent and/or pharmaceutical grade chemical or biological agents; receipt of agents from suppliers; safe and stable storage; accountability for receipt, storage, study allocation, & shipment; support, as needed and compliant with cGMP and FDA IND regulations, for bulk and formulated drug method development & characterization, dosage formulation, encapsulation, release & stability testing, packaging and labeling, clinical study drug accountability, and documentation. Essential activities for the overall operation include: inventory control to ensure timely reordering, forecasting of agent shipments, materials orders, and capacity required, shipping of agents, maintenance of up-to-date records of shipments, and analytical and quality assurance capability. Agent-related regulatory activities include developing and assembling documentation for the Chemistry, Manufacturing, & Control section of an IND and/or a Drug Master File and special analytical and pharmacological tests as required for drug development and/or by the FDA.

Rapid Access to Preventive Intervention Development (RAPID) Program as well as other preclinical and clinical projects require number of agents (chemical and biological) which are not commercially available. Therefore, custom synthesis or manufacture (including isolation and purification from natural sources) are required. Approximately 25 agents per year require procurement via a custom synthesis/manufacture mechanism. For example, some of these may involve multi-step chemical syntheses, preparation of vaccines, cultivation of natural product for subsequent extraction and purification of desired substances, etc. Therefore, the contractor shall identify and pre-screen prospective companies for these tasks and select those deemed capable of delivering requested substances of appropriate purity and in timely and cost effective manner. In order to achieve this, the contractor shall implement appropriate subcontracts with these companies specifying the terms including item(s), purity, documentation and delivery date. The contractor shall evaluate documentation from the supplier to ensure that the conditions of the contract are met. Documentation should include a description of the analytical method used to characterize the identity and purity of the substance. The contractor shall independently confirm identity and purity of the procured substances as deemed appropriate after consultation with the Project Officer.

Many of the substances have unknown stability profile and need to be tested periodically for occurrence of degradation. Some substances need a formal stability testing program while occasional non-GLP purity testing would be more practical and appropriate for others. The contractor shall propose a testing system for occasional non-GLP testing of substances in the repository. In many cases, reference compounds may not be available and it may be possible to check for degradation by comparison of a chromatogram (preferably HPLC or LC/MS) to archived chromatogram (from the supplier, literature, or chromatogram generated on receipt of the substance) under comparable conditions.

Approximately 100 active preclinical contracts involving multiple *in vitro* screening, animal model studies, and toxicology studies are in progress by the NCI DCP. Ten to 25 such studies are planned to begin each year. These studies, especially the short term *in vitro* evaluations, shall require a variety of small gram and milligram quantities of agents. It is expected that the animal model & toxicity studies shall encompass as many as 30 agents being given to thousands of animals at 20 different centers throughout the world, primarily continental United States. In addition, there are presently approximately 90 NCI DCP-supported clinical trials involving some dozen agents and 100,000 research subjects located at 50 different centers throughout the world, and additional studies are planned. These clinical studies represent a multimillion dollar investment, not only in clinical trials research, but also in the cost of agents. It is essential, therefore, that the supply of agents to these studies is uninterrupted and that alternative plans for agent supplies be in place as a standard operating procedure. There shall be no interruption in the supply of agents to study sites. There is also a need for information on the availability of these compounds so that other investigators

outside the supported studies can obtain compounds in order to further stimulate development activities in the cancer chemopreventive area. Thus, there is a need for a centralized location with standardized formats for obtaining bulk chemopreventive reagents, receiving, handling, packaging, distributing, storing, and monitoring stock levels for these agents. Inventory control procedures are a critical element in coordinating these tasks. The contractor shall be responsible for maintaining an up-to-date Oracle-based inventory management system that is compatible with and interfaced to the DCP's Enterprise System Knowledgebase (DESK). This electronic inventory system shall have an appropriate levels of security and be accessible to appropriate DCP personnel and their designates remotely.

It shall be the responsibility of the new contractor to assume all costs associated with the transfer of all government owned material and equipment to the new contractor site.

The Contractor shall be responsible for assuring that adequate and appropriate storage of drugs and chemicals required for chemoprevention testing are never exhausted and, therefore, the course of clinical and preclinical drug development proceeds in an uninterrupted manner.

A. Facility and Organizational Operations

The Contractor shall establish a Centralized Chemoprevention Agent Repository and Distribution Facility that should contain approximately 10,000 ft^2 dedicated to this project.

The project generally requires:

1. Principal Investigator (PI) with appropriate technical, scientific, managerial and business skills and background to manage the repository with input and instructions from the Project Officer, as needed.

2. Maintenance of organized, complete and current information on all projects such that a temporary or permanent replacement for the PI can continue uninterrupted operation of the repository, in case it becomes necessary.

3. Properly trained back-up for the PI in case PI becomes temporarily or permanently unavailable.

4. Licensed pharmacist on staff in order to make interstate shipments.

5. Properly trained repository personnel and internal QC/QA for the repository operations and data.

6. Weekly electronic report (spreadsheet or database) to the Project

Officer with complete, accurate and up-to-date information on the status of all on-going projects including procurement, receiving and shipping.

7. Provision for electronic ad-hoc queries by the Project Officer and designees reporting the status of all on-going projects including procurement, receiving and shipping.

8. Identification of agent (chemical or biological) suppliers, inquiry as to purity, availability, cost, and schedule of supply.

9. Capability for formulation, packaging, labeling, release and stability testing.

10. Maintenance of a list of suitable custom synthesis companies, keeping records of their performance in terms of product quality, timely delivery, adequate and appropriate documentation, and cost.

11. Writing of appropriate contracts with subcontractors and custom synthesis companies specifying deliverables (item, quantity, quality, documentation), delivery schedule, and conditions.

12. Audit and site visit (as necessary) of agent suppliers and custom synthesis companies to ensure technical competence, proper document availability and archival, and appropriate business practices..

13. Procurement of most of bulk agents (chemical or biological) for preclinical and clinical studies.

14. Receipt of agents from various suppliers.

15. Safe and stable storage until requested by the Project Officer,

16. Planning and directing the repackaging of agents directly or by subcontractors to meet user needs.

17. Shipping of agents (appropriately packaged to ensure stability and prevent physical damage) to users with appropriate characterization data and handling instructions.

18. Shipping of agents to subcontractors for special formulation and/or packaging before shipment to final destination.

19. Quality assurance capability for checks on purity of bulk agents.

20. Capability for shelf-life determinations of agents directly or through subcontactors.

21. Capability for more complete chemical analysis of agents to generate Certificates of Analysis.

22. Capability of periodic analytical retesting of agents in stock to confirm the results of Certificate of Analysis and a lack of agent degradation.

23. Capability for monitoring agent quantities in storage and at user locations.

24. Capability for inventory control and tracking system to ensure timely reordering, processing and shipping of material.

25. Accountability for shipping, receipt of returned agents, and destruction of unused, returned, expired agents, as per EPA, OHSA, DOT, etc. requirements.

26. Maintenance of up-to-date electronic records of agent sources, degree of readiness for testing, acquisitions, shipments, and reorders.

27. Maintenance of equipment and facilities in the accordance with local, federal and industry guidelines and regulations, including calibrations, testing, and log.

28. Capability for limited pharmacological evaluations, such as absorption, distribution, metabolism and elimination studies and special pharmacological requirements.

29. Acquisition of information, analytical data, and documentation for the Chemistry, Manufacturing, & Control section of INDs to the FDA (or the equivalent as a Drug Master File).

30. Methods development for analytical procedures.

31. Maintenance of relational database system for agent inventory, information, and distribution and its full integration with DCP's Enterprise System Knowledgebase (DESK) and remote access capability for DCP and its designates.

32. Secure off-site data back-up system with appropriate back-up scheduling.

33. Appropriate database and system recovery and restoration capabilities.

34. Capability for obtaining and archiving digital photographs of bulk agents and formulated products.

B. Equipment Requirements

The large number and volume of handling chemopreventive agents in various stages of development for preclinical and clinical studies requires specific equipment and capability for maintenance to be already available on site.

1. The Contractor shall possess the capability and resources for:

a) -70EC or lower UltraLow Temperature freezer (alarmed, operational log equipped and with appropriate back up plan in place)
b) -20EC to -10EC freezer room or equivalent (alarmed, operational log equipped and with appropriate back up plan in place)
c) 2-8EC cold room or equivalent (alarmed, operational log equipped and with appropriate back up plan in place)
d) Appropriate temperature and humidity controlled facility.
e) ice machine
f) dry ice supply (must be always readily and adequately available)
g) chemical fume hood
h) laminar flow hood
i) refrigerated centrifuge
j) chemical storage cabinets
k) storage capabilities in a controlled room-temperature environment
l) personal computers
m) facsimile telecommunication
n) appropriate software compatible with DCP applications, including but not limited to word processing (MS Word, Wordperfect), spreadsheet (MS Excel), database (MS Access, Oracle), document management and archival (full version Acrobat), graphical (Adobe Photoshop).
o) security system
p) fire suppression system
q) FDA-approved labeling
r) analytical balances (µg to kg)
s) weighing areas
t) inert gas supplies (N_2, Ar, etc.)
u) desiccators
v) suitable analytical instrumentation such as GC, HPLC, GC-MS, LC-MS, etc. some of which can be through subcontracts
w) readily available access to appropriate radioactivity use area and liquid scintillation counter. There is infrequent need for procurement, storage, and shipping of radioactive substances (3H or 14C), therefore this capability may reside elsewhere within the company but be readily available when needed infrequently or at a subcontractor.
x) appropriate lighting conditions for light sensitive materials.
y) secure computer system for inventory management and interfacing to DCP's Enterprise System Knowledgebase (DESK) and remote access

2. Retain small samples of finished agents or intermediates and store under appropriate stable and safe conditions for future reference and maintain complete information relating to them.

3. Possess direct or subcontracting capabilities for shelf-life determinations, analytical methods development, USP chemical analysis, experimental cGLP/cGMP formulations, hard tableting, hard and soft gelatin capsule filing, special pharmacological testing, labeling, and packaging in calendar, blister, or prescription packages/bottles.

4. Possess capability for cold storage (-4EC to -40EC or -70EC) of split-sample sera and other biological fluids and tissues from preclinical studies and clinical trials for time period covering period of performance.

5. Maintain, modify and update, as necessary and as requested by the Project Officer, an inventory system for tracking the activity of chemopreventive agents.

6. Interface with study directors, NCI staff, and drug/chemical manufacturers to insure against drug supply exhaustion at any study site.

7. Provide an information management system that is integrated with NCI DCP's Enterprise System Knowledgebase (DESK) with a secure remote access capability.

8. Maintain complete detailed documentation for the electronic information management system and any hardware and software upgrades, updates, patches, modifications, customizations, and fixes in order for other system operators and programmers for the contractor or a possible future contractor, to maintain it.

II. Specific Requirements:

A. Chemopreventive Agents for Preclinical Studies

Preclinical studies shall require source identification, acquisition, receiving, shipping, distribution and monitoring of stock levels for the given agent(s). These activities shall, in most cases, be undertaken in their entirety by the contractor. Subcontractors of the drug repository shall be responsible for special formulations, encapsulations of formulations, and any repackaging of these agents for delivery. The contractor shall be responsible for routing and monitoring the flow of agents through these intermediate steps including the shipment of processed agents to their final destinations. **The contractor shall receive approval (hardcopy or electronic) before shipment of agents to users from the Project Officer or designate.** It is anticipated that up to 30 agents per year shall be involved in these studies, e.g., some that are currently under consideration are: arachidonic acid

modulators, anti-proliferatives, anti-oxidants, & anti-mutagens, aromatase inhibitors, inducible nitric oxide synthetase inhibitors, EGFR inhibitors, retinoid X ligands, deacetylase inhibitors. Each preclinical study shall involve administering agents to several hundred animals for three months to two years. Most shall require shipping one or more agents to user sites. There could be as many as 20 different geographical sites in the continental U.S. requiring agents.

1. Specific Requirement for Preclinical In Vitro Screening Studies

a) Project Officer shall select 25-200 potential chemopreventive agents per year and forward information to contractor for source and price analysis

b) Contractor shall identify 3-5 sources of 25-200 potential chemopreventive agents and perform comparative price analysis for bulk agent purchases

c) Contractor shall prepare inventory list on 25-200 agents. This list shall contain information on:

(1) suppliers, lot number, purity, form (salt, free acid or base, counterion), molecular weight, melting point, solubility;

(2) material data safety sheets, handling and storage instructions, stability data

d) Contractor shall purchase material, receive agents, enter agents into inventory system, and prepare testing kits for shipping agents to preclinical in vitro study sites; kits shall contain vials (1-4 g light sensitive glassware) labeled with inventory information.

e) Contractor shall physically transfer and accurately weigh small quantities of agents to vials.

f) Contractor shall ship kits and inventory information to study sites.

g) Contractor shall monitor kits and agent supply by interaction with study directors and Project Officer.

h) Contractor shall retain 1 g sample for future testing and store agents in warehouse under appropriate safe and stable conditions.

2. Specific Requirements for Preclinical In Vivo Screening Studies

a) Project Officer shall select 25-150 potential chemopreventive agents per year and forward information to contractor for source and price analysis.

b) Contractor shall identify 3-5 sources of 25-150 agents and perform comparative price analysis.

c) Contractor shall inform Project Officer of sources, quantity, FDA status, lot, purity, solubility, melting point, and prepare inventory list that includes information on material data safety sheets, handling instructions, and stability data.

d) Project Officer shall indicate agents to be purchased by the contractor in bulk 2-10 kg quantities

e) Contractor shall purchase agents and coordinate purchase and quantity needed for study with study director and Project Officer.

f) Contractor shall receive agents, enter agents into inventory system, and allocate quantities of agents into appropriate transfer receptacles for shipping to study sites.

g) Contractor shall label receptacles appropriately with inventory information.

h) Contractor shall ship agents to study sites along with inventory information and monitor need for additional supplies.

i) Contractor shall reserve 1 g sample of agents for future analysis and store agents in warehouse under appropriate safe and stable conditions.

j) The contractor shall procure and retain a Certificate of Analysis for purchased agents.

3. Specific Requirements for Preclinical In Vivo Efficacy Studies

a. Project Officer shall select 10-50 potential chemopreventive agents per year and forward this information to contractor for source and price analysis of 4-12 kg of each agent.

b. In vivo efficacy chemopreventive agents shall be handled, otherwise, identically to those procedures described above for in vivo screening agents.

4. Specific Requirements for Preclinical Toxicology Studies

a. Project Officer shall select 5-15 agents for preclinical toxicology studies per year and forward this information to the contractor for source and price analysis for 10-30 kg of each agent.

b. Preclinical toxicology agents shall be handled by the contractor identically to those procedures described above for in vivo screening studies.

B. Coordination of Chemopreventive Agents for Clinical Trial Studies

With regard to clinical studies, the contractor shall be assigned responsibilities for the agents presently being utilized in 90 on-going clinical trials. These trials already have agents in their possession but shall need additional shipments during the course of the studies. The contractor shall purchase bulk reagents for chemoprevention research when necessary and after approval to do so by NCI. In addition, the contractor shall establish procedures both for interfacing with pharmaceutical, nutritional, and chemical industries and obtaining chemopreventive agents from industries. The contractor shall be required to implement inventory monitoring procedures and phase-in the designated tasks which would maintain a timely flow of the appropriate agents needed for these on-going studies. It is anticipated that approximately 5-10 new trials shall be added each year from 40 to 30,000 subjects receiving one or more agents each day for several months to five years. It is anticipated that medium size clinical trial populations shall predominate over very large clinical trials, particularly those involving over 10,000 subjects. These data are presented for information purposes only. There may be several finishing steps involved prior to agents being ready for clinical trials. This may require shipment of agents to various subcontractors for completion of these intermediate steps. These steps might include dosage formulation, encapsulation, packing in suitable containers such as calendar packs, labeling and shipment to the user site. While dosage formulation, encapsulation and packaging shall be undertaken by subcontractors, implementing and monitoring the flow of these aspects together with final labeling and shipping to final destination shall be the responsibility of the primary contractor. **The contractor shall receive approval (hardcopy or electronic) before shipment of agents to users from the Project Officer or designate.**

1. General Requirements for Clinical Trials

a. Contractor shall identify sources of chemopreventive agents and analytical reference materials (and metabolites of drugs when appropriate), and prepare comparative price analysis as requested by the Project Officer.

b. Contractor shall purchase, receive and store bulk chemopreventive agents, and their metabolites and analytical reference materials at the

request of Project Officer and enter appropriate information into inventory management system.

c. The Certificate of Analysis and any other documentation of purity shall be obtained and retained by the Contractor.

d. Contractor shall identify steps necessary for finishing agents or pharmaceutical products and coordinate shipments to subcontractors for finishing.

e. Contractor shall receive, label, store and coordinate shipments of agents to study sites at request of Project Officer.

f. Contractor shall retain and store under appropriate conditions small quantities (grams) of finished agents sent to study sites.

g. Contractor shall acquire and store placebo pills and maintain codes of active and placebo bottle numbers for blinded studies.

h. Contractor shall assist with preparation of Investigational New Drug Applications and with the filing of annual reports under each approved application.

i. Contractor shall possess subcontracting capabilities for shelf-life determinations, USP analysis of drug constituents, experimental formulations, hard tablet preparations, hard and soft gelatin capsule preparations, microbial, metal, & residual solvent analyses, labeling and packaging in calendar or blister packs or prescription bottles.

j. Contractor shall provide technical support for the development and filing of the Chemistry, Manufacturing, & Control section of IND=s (or Drug Master Files) with the FDA.

k. Contractor shall obtain from manufacturers the Investigators Brochure on a potential chemopreventive agent.

l. Contractor shall provide a written analysis of any additional analytical chemistry studies of agents designated for human evaluation in a chemopreventive setting.

m. Contractor shall supply freezer and cold-room space for appropriate storage of biological fluids and/or tissues samples conducted at study sites.

n. Contractor shall coordinate receipt, storage and shipping of split-samples of biological fluids and/or tissues with study directors, the Project Officer, and subcontractors.

o. Contractor shall possess capability for long-term storage (#70EC) of biological fluids and/or tissues.

2. Specific Requirements for Handling Agents for Phase 1 Trials

a. Project Officer shall execute 3-5 new phase 1 studies per year and forward information on the status of these studies to the contractor.

3. Specific Requirements for Handling Agents for Phase 2 Clinical Trials

a. Project Officer shall execute 5-10 new phase 2 double-blinded, randomized studies per year and forward information on the status of these studies to the contractor.

b. Contractor shall identify sources for and prepare comparative price analysis for reagents that are useful in examining intermediate markers and as indicators of premalignant neoplasia. Such reagents could include commercially available monoclonal antibody reagents for oncogene/tumor suppressor genes, cell receptor proteins, etc. They might also include specific substrates for enzymatic studies, hormones, etc.

4. Specific Requirements for Handling Agents for Phase 3 Clinical Trials

a. Project Officer may evaluate 1-3 new agents per year in phase 3 intervention and this information will be forwarded to the contractor. The studies may involve double-blinded randomized clinical evaluations of chemopreventive agents in high risk populations with tumor latency, multiplicity, tumorigenicity, morbidity and cancer mortality as end points.

b. Capability, if necessary, to coordinate/manage distribution for large clinical trials sponsored by other NCI divisions or outside groups.

B. Chemopreventive Agent Tracking Activity

1. The preclinical and clinical studies shall be conducted by other contractors at their designated sites, however, the aspects of drug sources, drug receipt, stability testing, repacking, storage, monitoring stock levels, quality control, shipment to subcontractors for formulation and special packaging, and shipment to final user destinations shall be the responsibility of this contractor. It is essential that the NCI-supported preclinical and clinical studies, which this contract shall service, not run out of experimental agents. Interruption in the drug supply to a study could result in not only costly delays, but might invalidate the entire study. Therefore, identification of alternative sources of agents and possible procurement of bulk reagents, monitoring procedures,

inventory control and adequate safety stock levels are critical tasks to be performed by this contractor.

2. The centralized repository shall obtain, store, handle, ship, and track the activity of chemopreventive agents in various stages of development. It is imperative, therefore, that consistent and valid measures for routine operations be carefully designed and that alternative procedures be in place for handling emergencies.

3. The Repository Contractor shall have in place procedures and standard mechanisms of operation for:

- agent source identification
- obtaining agents
- receiving agents
- agent storage procedures
- agent handling procedures
- forecasting materials orders and capacity requirements
- shipping agents
- storing agents and biological fluids and tissues
- finishing agents
- safety procedures
- managing inventory at study sites and in the warehouse
- tracking agents on test
- packaging and repackaging agents
- perform price analysis on alternative sources of agents
- phasing-in and interfacing procedures for assisting with studies
- drug auditing
- labeling agents
- reordering agents
- disposal of expired, returned, unused agents
- subcontracting capabilities for:
  i. USP chemical analyses
  ii. stability and shelf-life determinations
  iii. mutagenesis screening
  iv. tableting
  v. hard and soft gelatin capsule
  vi. preparation and filling
  vii. special pharmacological tests
  viii. method development and absorption/distribution/metabolism/elimination (ADME) measurements
  ix. synthesis
  x. formulation and preparation of placebos for clinical trials

4. The contractor or subcontractors shall have experimental drug formulation capability including:

    a. solid preparations
    b. soft elastic gelatin encapsulation
    c. time-release preparations
    d. microencapsulation
    e. vaginal tampons and cervical sponges
    f. rectal suppositories
    g. transdermal implants and/or osmotic pumps
    h. topical creams and lotions
    i. aerosols for inhalation
    j. injectable vaccines

5. The contractor shall have licenses and permits required for the storage and distribution and disposal of chemicals and investigational substances which may be required depending on regional jurisdiction

    a. documentation of conformance to current Good Manufacturing Practices
    b. chemical and drug disposal mechanism
    c. procedures for assisting program with gathering and preparing CMC / DMF documents
    d. safety and emergency protocols for staff and agents.
    e. license to handle radioactive materials

D. <u>Synthesis of Chemopreventive Agents Activities</u>

1. Project Officer will inform contractor of agents to be synthesized, formulated, encapsulated, tableted, or other forms prepared by other contractors.

2. Contractor shall coordinate procurement and receipt of agents to be encapsulated, tableted, formulated from subcontractors.

3. Contractor shall receive agents, enter agents into inventory management system, and store agents under appropriate safe and stable conditions.

4. Contractor shall ship agents, bulk materials or synthetic intermediates together with inventory and handling information to subcontractors for finishing as final pharmaceutical products.

5. Contractor shall receive, inventory and appropriately store all agents finished as final pharmaceutical products.

E. Source Identification, Price Analysis, Receiving, Repackaging, Shipping, Distribution and Quality Control Measures

1. All work must be performed in accordance with FDA's established current Good Manufacturing Practices.

2. The contractor shall develop a standard operating procedure for identification of sources of chemopreventive agents. This shall include identification of bulk quantities, purity, and price comparison of agents available through international suppliers. The contractor shall include in the price analysis detailed statements on patent status and pharmaceutical steps required to produce a finished pharmaceutical product. The contractor shall interact with subcontractors to obtain information pertinent to these goals, i.e., dosage, formulation, chemical stability, etc. Should the latter information not be readily available, the contractor shall obtain the necessary pharmaceutical and chemical information from the supplier or reference material.

3. The contractor shall purchase chemicals and drugs under the following guidelines:

    a. The contractor shall seek competition for all purchases of chemicals and drugs performing a price analysis on all acquisitions between $3,000 and $25,000 (see individual specific requirements stated above).

    b. Sole source acquisitions and those acquisitions costing over $25,000 shall be processed by NCI.

    c. The contractor shall proceed with a given purchase only upon written approval by the Contracting Officer.

4. The contractor shall receive, package and ship chemicals and drugs as requested by the Project Officer, or as indicated by just in time supply analysis and approved by the Project Officer, to research investigators in the U.S. and throughout the world so that such shipments are received in a timely fashion. The contractor shall be responsible for keeping up-to-date with all regulations, including U.S. and foreign customs regulations, concerning transport and receipt of these chemicals and drugs. The contractor shall implement standard operating procedures to assure obedience to federal laws governing investigational substances.

5. The contractor shall provide chemical laboratory facilities and equipment necessary for repackaging bulk agents into smaller containers, generation of FDA-approved labels for small (Phase 1 or 2) and occasionally larger phase 3 double-blind randomized clinical trials, and capabilities for preparation of hard tablets, pilot formulations, and quality control chemical analysis.

6. The contractor shall provide special storage and handling for heat sensitive, photosensitive, and other types of labile chemicals and drugs.

7. The contractor shall conform to all laws and regulations governing the shipping of hazardous substances and/or drugs.

8. The contractor shall furnish shipping cartons, cushioning materials, labels, containers, insulating material, dry ice and other supplies to insure the safe, intact arrival of the contents of each package shipped.

9. The contractor shall be responsible for providing inventory transactions, the documentation of the shipments of compounds, and other such data.

10. Foreign shipments may include, but not limited to the following countries at this time: England, China and Italy. Other foreign projects can be expected, but are unknown at this time. About 5% of all activities shall

involve coordination and shipment of agents to foreign investigator and shall require knowledge and/or understanding of foreign customs and/or pharmaceutical agencies, food and drug laws and/or regulations. The contractor shall provide all required labels and obtain export permits as needed.

11. The contractor shall send notification by cables/telegrams/facsimiles/Email to all foreign investigators receiving shipments. Telephone notification shall be made by the contractor to all domestic laboratories receiving shipments.

12. The contractor shall be responsible for all equipment calibration, repair and maintenance.

F. Storage of Chemopreventive Agents

1. The contractor shall receive investigational compounds together with their documentation from various chemical and drug companies and from acquisition contractors as arranged by NCI.

2. The contractor shall provide facilities for proper storage of chemicals, bulk compounds and bulk clinical drugs.

3. The contractor shall store the chemicals, possibly biological fluids/tissues and drugs separately under their required storage conditions (frozen, refrigerated, controlled room temperature, light protected, etc.). The contractor shall also maintain security of all storage facilities and provide sufficient monitoring of such storage conditions including an alarm system to guarantee continuous proper storage.

4. The contractor shall provide safe handling of toxic and potentially hazardous materials and security measures to conform to all pertinent drug and chemical regulations. Contractor staff shall employ appropriate chemical safety procedures at all times.

5. The contractor shall provide and maintain relevant, accurate, and current records for all bulk chemicals in stock, such as identity, amounts, inventory and shipping history.

6. The contractor shall maintain reference samples of all compounds in a readily accessible location and in a manner in which they can be easily identified.

7. The contractor shall physically update the inventory of all chemicals and drugs at the repository and at user sites on a monthly basis and enter in into the electronic agent inventory system and make this information available to the Project Officer.

8. The contractor shall provide local transportation for package pick-up, package receipts and package deliveries.

9. The contractor shall process returned chemicals and drugs and provide for the proper disposal of them as designated by the Project Officer and in accordance with regulations.

10. The contractor shall possess capability and appropriate staff to conduct cGMP audits and site visits as specified by and accompanied by the Project Officer and/or NCI staff.

G. Information Management System

1. The contractor shall maintain and support the present chemical and drug inventory and distribution record information management system, Oracle-based relational database Preventive Agent Management System (PAMS). Since most agents shall be regulated under Investigational New Drug applications (INDs), the contractor shall preserve this data for at least two years post-termination of an IND. The contractor shall preserve data related to non-IND agents for a period of time specified by the Project Officer. This information shall be stored electronically and made available when requested to the NCI project officer or its designate(s).

2. If awarded to a new contractor, the new contractor shall transfer PAMS to its own computers and ensure its full functionality and provide appropriate support, updates, upgrades, and enhancements. Contractor shall maintain appropriate documentation and ensure full portability of PAMS.

3. The contractor shall maintain and enhance standard procedures for information management for chemopreventive agents and chemicals with potential chemopreventive activity. These procedures shall include coding agents and chemicals, lot numbers, industrial contacts, patent status, manufacturers and suppliers, sample numbers, packing, shipping, and receiving status, and any additional information approved by the Project Officer pertinent to finishing an agent for chemopreventive evaluation.

4. The contractor shall enhance and extend PAMS or design and implement a new PAMS System to meet the additional requirements specified in this section. If a new system, it should incorporate all

existing functionality of PAMS. (Existing functionality of PAMS is provided in the PAMS functional specification attached as an addendum to this SOW.) The requirement under this contract is that any new source code developed be open source and based on de jure or de facto standards. Deviation from this requirement should be identified in the contractor's response to this RFP.

5. The contractor shall integrate PAMS with the DCP Enterprise System Knowledgebase (DESK) and ensure that PAMS provides data to support DESK users.

    a. The contractor shall ensure that PAMS is fully interfaced with the DCP Enterprise System Knowledgebase (DESK) and have a remote access capability for DCP and its designees. Data must be shared between PAMS and DESK in an automated, labor-free process. The process shall not involve duplicate storage of the same data in both PAMS and DESK. DESK data to be utilized by PAMS include, but are not limited to, address data, agent data, clinical trials data, pre-clinical study data, and contracts data. Data sharing between the PAMS and DESK shall not require a manual reconciliation process.

    b. The contractor shall ensure, to the extent possible, that PAMS uses the presentation layer and user interface that is standard across all new DESK applications. Deviation this requirement should be identified in the contractor's response to this RFP.

    c. The contractor shall ensure that PAMS provides DCP personnel and their designees the capability to perform ad-hoc queries of information in PAMS and related information in DESK. Such queries would include, but are not limited to, quantity of material in inventory, expiration dates of inventory, status of stability testing processes, shipment status, and analytical information supporting IND applications.

    d. The contractor shall maintain and update/upgrade/enhance standard procedure for information management for chemopreventive agents and chemicals with potential chemopreventive activity. This procedure shall include coding agents and chemicals, lot numbers, industrial contacts, patent status, manufacturers and suppliers, sample numbers, packing, shipping, and receiving status, and any additional information approved by the Project Officer pertinent to finishing a pharmaceutical for chemopreventive evaluation. PAMS shall utilize chemopreventive agent data already stored in DESK wherever possible rather than duplicating data already stored in DESK.

6. Taking into account the current constraints in time to acquire new proprietary agents from pharmaceutical manufacturers, the contractor shall still ensure PAMS maximizes, to the extent possible, the quality and efficiency of the entire supply chain from ordering of bulk materials through delivery to study sites, to return and destruction of unused agents.

    a. The contractor shall ensure that PAMS supports supply chain management for the commercially available materials handled by the repository. (However, it should be recognized that commercially available agents constitute a very small fraction of agents in the inventory. Most of these agents are a product of custom synthesis, isolation, purification, and/or formulation or supplied as clinical study products (active and placebo) by pharmaceutical collaborators. As such, their acquisition and/or processing requires a large lead time.) Supply chain management is the optimization of the entire fulfillment process, from consumption back through delivery, order, inventory, coding, packaging, formulation, testing, bulk supply, etc. for greater responsiveness, speed and efficiency. Aspects of supply chain management to be supported by PAMS include:

        i. Materials Requirements Planning and Forecasting: The system will regularly analyze indicators of delivery requirements (participant accruals, protocol design, inventory shipped, lead times, etc.) in order to forecast the raw materials orders and the testing, manufacturing, packaging, coding and inventory capacity needed to meet the delivery requirements.

        ii. Inventory Management: The system will monitor the inventory in the warehouse to insure that shipments to preclinical and clinical studies are uninterrupted.

        iii. Quality management: Performance metrics will be developed and implemented that span the entire supply chain, and the system will support regular collection, tracking, and audit of those metrics.

    b. The contractor shall monitor and closely track supplies of agents in storage in order to reship additional chemicals or to alert NCI to the need for additional acquisition of chemicals in a timely manner. It is imperative that adequate supplies and shipments of chemicals are tightly coordinated to insure that the preclinical and clinical studies are uninterrupted.

c. The contractor shall design PAMS so that agents may be easily identified under all common synonymous names, ensuring that agent supply is not interrupted when the needed agent exists in the repository but is stored under a name not specified in the protocol.

d. The contractor shall ensure that PAMS allows site pharmacists or their approved designees to request drug shipments within the system, without requiring fax, verbal, or telephone requests. PAMS must store and reproduce appropriate the documentation required to report and audit agent shipment requests. This feature will require web-based access to PAMS capable of supporting data entry at study sites.

e. The contractor shall enhance existing PAMS data quality control procedures to ensure high quality, integrity and consistency of all PAMS and DESK data. This includes the development of appropriate, automated edit and validation rules for data cleansing and production of regular exception reporting to identify potential issues with quality of specific data elements. The contractor will also provide user documentation, standard operating procedures, and user training to support PAMS data abstraction and quality control activities

f. PAMS shall automatically notify the contractor of regulatory triggers and milestones relevant to drug and biological material supply. These types of milestones include DCP receipt of an FDA-approved Form 1572 for an investigator, and pending expiration of supplier agreements.

7. The contractor shall ensure that PAMS conforms and integrates with appropriate industry standards and NCI technology infrastructure.

a. All messages between PAMS and external systems should be based on HL7 messaging standards, preferably HL7 3.x (XML) version of standard. Deviation from this requirement should be identified in the contractor's response to this RFP.

b. The contractor shall ensure that data used by PAMS complies with the National Cancer Institute's Cancer Data Standards Repository (caDSR) metadata standards, and that all data are represented as Common Data Elements approved by DCP. To the extent that PAMS data does not come directly from DESK, PAMS shall be integrated with the caDSR so that Common Data Element metadata may be accessed directly from PAMS wherever appropriate.

c. To the extent that PAMS data does not come directly from DESK, the contractor shall ensure that PAMS is fully integrated with the NCI Enterprise Vocabulary Services (EVS) and will use EVS as the source of terminology wherever possible. Specifically, the contractor shall use the CaBIO API to access EVS services, and shall implement an e-mail-based mechanism for PAMS users to requests changes to EVS content.

d. PAMS shall provide an indicator that identifies whether or not an agent is proprietary. All non-proprietary agents should be identified using EVS concept codes in addition to any other codes or identification that may be required. All proprietary agents must indicate an agent's UNII code. (UNII is a soon-to-be-released FDA coding system for new compounds.)

8. PAMS shall keep a complete audit trail of all changes to any data stored within PAMS. Regular reporting of audit trail changes must be provided.

9. The contractor shall ensure that PAMS is capable of supporting a large base of concurrent users (up to 100) via a web-based user interface. The web-based interface must support both inquiry and data entry at study sites.

10. PAMS system performance must be readily accessible to multiple simultaneous users without a significant degradation in performance, so that for most data entry and inquiry functions, this means near immediate response time.

11. Contractor shall have appropriate, experience database management, programming and other technical personnel on its staff to provide support and maintenance of PAMS. Contractor shall also have appropriate Oracle licensure prior to the actual start of the contract in the event PAMS will need to be transferred.

12. Contractor shall utilize TestTrack Pro or a comparable tool to track PAMS bugs, issues and change requests. Remote web access to the tool and its contents should be provided to NCI-designated representatives.

13. In addition to PAMS, contractor shall provide a Laboratory Information Management System (LIMS). An open source solution is available from NCICB free of charge. Please see **http://lpglims.nci.nih.gov/** for more details. The LIMS should be fully integrated with PAMS and DESK.

14. The contractor shall ensure that PAMS complies with 21 Code of Federal Regulations Part 11, the FDA regulations regarding electronic records and signatures, as well as other applicable regulations and laws. 21 CFR 11 and current guidance are found at **http://www.fda.gov/ora/compliance_ref/part11/.**

15. The contract shall participate as subject matter experts in other DCP and NCI informatics design and development activities, as directed by the project officer. This may include attending "knowledge acquisition" sessions to define requirements and data model reviews, and participating in user testing efforts for DESK enhancements and other systems.

H. Security and Safety of the Agents

1. The majority of the chemicals and drugs to be stored and distributed are obtained from commercial sources. All information relating to such material is to be regarded as confidential and treated as such.

2. The contractor shall not be authorized to divulge any information beyond handling instructions (Material Safety Data Sheets and Certificates of Analysis) which shall be sent with the agent unless otherwise authorized by the NCI Project Officer. All inquiries must be directed to the Project Officer.

3. The contractor shall be expected to comply with all security and safety requirements and regulations applicable to federal, state, and other jurisdictions such as foreign countries, if that is a point of destination.

4. Personnel assigned to this project must be bondable.

5. The area storing the chemicals shall be protected against fire by systems other than water sprinklers. This system must be approved by the county Fire Marshall and updated accordingly.

6. Clinical trials require that agent identity be coded and that only certain designated individuals have access to encoded information. Ordinarily, this shall be done by qualified individuals at the clinical trials facilities who shall provide these data to this contractor who shall then, in turn, prepare the appropriately coded labels. In some cases, the contractor may be required to assist in the implementation of the blinding procedures and shall insure the integrity of the blinding at all times.

7. Approximately 5,000 ft^2 each should be available and totally dedicated for physically separate repository functions supporting clinical (i.e., IND-sponsored) and preclinical material. Both areas should possess security and Halon fire extinguishing systems, other than water sprinklers. The preclinical area shall possess a chemical fume hood and laminar flow

hood for chemical preparations. Nitrogen or other inert gases (argon) shall be available on site for flushing containers of agents with uncertain stability. The repository spaces for clinical and preclinical activities shall be contained in a free-standing or detached building. The building shall be located in a geographical setting zoned for industrial and not commercial practices.

I. Regulatory-Scientific Support Activities

1. Regulatory support to the CADRG shall include the development of standardized methods development for chemical analysis, preparation, and documentation of synthesis and formulations.

2. The contractor shall undertake the documentation preparation for final submission of up to 4 Chemistry, Manufacturing, & Control IND sections (or equivalent Drug Master Files) per year. The contractor shall be responsible for the acquisition and/or generation of necessary analytical data and shall compile information from various sources including manufacturers, government agencies, and government contractors and scientific literature. The contractor shall review the acceptability of materials in accordance with requirements and where necessary identify where additional information is necessary.

3. Provide expert technical assistance through in house personnel and consultants in such areas as analytical chemistry (including pharmacokinetic methodology), drug and metabolite synthesis, and regulatory aspects of medicinal chemistry.

4. Assure that the ingredients and dosage forms meet USP, NF, or other appropriate compendial standards, and to the extent possible assure that these various operations are conducted in accordance with FDA cGMP regulations.

5. Arrange for performance of appropriate analytical efforts to develop and validate drug quality (reference standards, identity, purity, potency), appropriate specialized analyses, and product stability methodology (shelf life and degradation testing protocols).

6. Provide scientific support for and attend Agent Development Committee meetings, as scheduled at the NCI. Scientific support would include agent suppliers, availability, formulations, dosages, analytical methods, synthesis methods, patent status, purity, stability, pharmacology, and regulatory status.

[END OF BACKGROUNG/STATEMENT OF WORK]